REMARKS

Claims 1-38 are pending the present application. Claim 1 has been amended to recite that the BPD/OFD ratio and the at least one secondary marker measurement are determined at a same trimester of pregnancy. Support for this amendment can be found on page 42, where the BPD/OFD ratio and the secondary marker measurements were taken during the same trimester of pregnancy. Claim 1 has also been amended to recite that the fetal abnormality is a chromosomal abnormality, a craniofacial abnormality, or a developmental central nervous system abnormality. Support for this amendment can be found in paragraph 15 (page 5, lines 22-25 and in Table 1). Applicants point out that open spinal bifida is a developmental central nervous system abnormality as it is a neural tube defect. Claim 4 has been amended to add the trisomic abnormalities of trisomy 13, and 18. Support for this amendment can be found in Table 1. Claim 5 has been amended to provide proper antecedent basis. Claim 28 has been amended to add "and" after the second to last method step. Support for new claims 31-38 can be found in Table 1.

Applicants also submit a replacement drawing of Figure 1, which has been amended to indicate that the bi-parietal diameter is the distance between B1 and B2 and the occipto-frontal diameter is the distance between A1 and A2. Support for this amendment can be found in the specification in paragraph 14.

Objections to the Specification

The specification was objected to because of two spelling errors. These spelling errors have been corrected and Applicants request withdrawal of these objections.

Objection to the Claims

Claim 1 was objected to for not reciting the full term "BPD/OFD ratio." Claim 1 has been amended to recite that the BPD/OFD ratio refers to the bi-parietal diameter to occipito-frontal diameter. As such, Applicants request withdrawal of this objection.

Rejection of Claims Under 35 U.S.C. 112

Claims 1-30 stand rejected for allegedly lacking enablement. The Examiner acknowledges that the specification is enabling for assessing a patient's risk of having a fetus with Down Syndrome or spinal bifida. In this regard, Applicants request clarification as to why original claims 4 and 5 were rejected for lack of enablement as these claims specified that the fetal abnormality is Down Syndrome and open spinal bifida, respectively.

The Examiner states that the specification does not reasonably provide enablement for assessing a patient's risk of having a fetus with any fetal abnormality. As recited by the claims and specifically defined in the specification, the fetal abnormality is not any fetal abnormality but is any developmental central nervous system abnormality, craniofacial abnormality, or chromosomal abnormality where the BPD/OFD ratio can serve as a marker. Particular examples of disorders falling within these categories are listed in the specification (i.e. trisomy 18, trisomy 13, trisomy 21, Turner's Disorder, open spinal bifida) and other disorders falling within these categories are well known in the art. The Examiner mentions that the specification does not provide examples for assessing the risk of having PKU or Tay-Sachs disease. However, such disorders are genetic mutation disorders, and do not fall within the specific fetal abnormalities recited in the claims.

The Examiner also states that the specification lists several fetal markers such as those for trisomy 13, 18, 21, open spinal bifida, Turner Syndrome, but does not describe which markers may be used in conjunction with the cephalic index for any of these defects. However, any of the listed markers (in addition to other secondary markers) can be used in conjunction with the cephalic index—that is the very point of the claimed invention, *i.e.* using the BPD/OFD ratio of the patient's fetus as a primary screening marker in conjunction with other secondary screening markers as part of a multiple marker screening protocol.

Rejection of Claims Under 35 U.S.C. 112-2nd Paragraph

Claim 1 has been amended to recite the step of determining the patient's *a priori* risk of having a fetus with a fetal abnormality and determining an at least one secondary marker measurement. As such, Applicants request withdrawal of the rejection of claim 1.

Claim 14 has been amended to include the steps of grouping the fetal BPD/OFD ratios and the at least one secondary marker measurements from the observed affected and the observed unaffected pregnancies into pre-determined categories of fetal BPD/OFD ratios and secondary marker measurements, respectively. Claim 14 clarifies that the first and second set of likelihood ratios are derived for each of the predetermined categories of fetal BPD/OFD ratios and secondary marker measurements, respectively. As such, Applicants request withdrawal of the rejection of claim 14.

Rejection of Claims Under 35 U.S.C. 103

Claims 1-30 stand rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent No. 6,573,103 to Wald ("Wald") in view of Stempfle et al Pediatric Radiology; Vol. 29, pages 682-688 (1999) ("Stempfle").

Claim 1 recites that the OFD/BPD ratio and the secondary marker measurement are determined at the same trimester of pregnancy. The very point of Wald is to take markers from two different stages of pregnancy. See Abstract ("Instead of using markers from a single stage of pregnancy, the method uses markers from two or more different stages of pregnancy, one being in the first trimester and another being in second trimester."). Therefore, even if Stempfle teaches that one marker can be a determination of the cephalic index (a point that Applicants are in no way conceding), Wald expressly teaches away from using such a measurement of the cephalic index with another marker, both from the same trimester of pregnancy.

With respect to claim 6, this claim recites that the OFD/BPD ratio is taken during the first trimester of pregnancy. As the Examiner recognizes, Wald does not teach or suggest measuring the OFD/BPD ratio, let alone measuring the OFD/BPD ratio in the first trimester of pregnancy. Further, Stempfle does not make up for this deficiency. Stempfle states in the introduction that ultrasound screening is particularly useful in the first trimester of pregnancy. However, Stempfle does not specifically state that

measuring the OFD/BPD ratio during the first trimester of pregnancy is useful. First, Stempfle's data relates entirely to data from 15-40 weeks of pregnancy, *i.e.* the second and third trimesters of pregnancy. Second, in the last sentence, Stempfle states that "bearing in mind that biological screening tests or maternal age indications detect only a minority of Down's Syndrome, we consider that these skeletal signs, when present at whatever gestational age, fully justify evaluation of the fetus by amniocentesis and cytogenic analysis." Importantly, Stempfle does not indicate that these skeletal signs justify chorionic villus sampling (CVS), an established first trimester diagnostic test. Given that Stempfle only included data from the second and third trimester and given the conspicuous lack of mention of CVS, Applicants assert that one skilled in the art would not be motivated to measure the OFD/BPD ratio during the first trimester of pregnancy, given Stempfle's disclosure.

Moreover, there is no evidence in Stempfle that measuring the OFD/BPD ratio during the first trimester is a reliable indicator of trisomy 18. As mentioned above, Stempfle's data is exclusively from the second and third trimesters of pregnancy and all the data was based on post-mortem analysis. Although Stempfle states that ultrasound screening is particularly useful in the first trimester of pregnancy, this is only the case if the ultrasound marker works. As one skilled in the art recognizes, just because an ultrasound marker works well at one point in pregnancy does not guarantee that it works well at another point in pregnancy, *i.e.* just because Stempfle shows data of the OFD/BPD ratio being an indicator of Down's Syndrome during the second and third trimester, does not mean that one skilled in the art would recognize that the OFD/BPD ratio is necessarily a reliable indicator during the first trimester.

Further, Stempfle specifically mentions that brachycephaly "was always associated with one or two other key skeletal signs," suggesting that it may not even be necessary to use the OFD/BPD ratio as a screening marker since other screening markers are available.

For at least these reasons, Applicants submit that the present claims are not rendered obvious by Wald in view of Stempfle and request withdrawal of this rejection.

CONCLUSION

It is respectfully submitted that the present application is now in condition for allowance, which action is respectfully requested. The Examiner is invited to contact Applicants' representative to discuss any issue that would expedite allowance of the subject application.

Any fees for extension(s) of time or additional fees required in connection with the filing of this response, are hereby petitioned under 37 C.F.R. § 1.136(a), and the Commissioner is authorized to charge any such required fees or to credit any overpayment to Kenyon & Kenyon's Deposit Account No. 11-0600.

Respectfully submitted,

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